hypertensive patients. Results of meta-analyses should be viewed with circumspection, especially when clinical practice might be influenced (2). With one-fifth of the general population susceptible to migraine (and other primary vascular headaches) and with nonvasodilating beta-blockers still regarded as first-line preventive agents, the conclusions of this study (1) raise concern. The authors admittedly ignore the dose of atenolol (1), a critical variable that limits this analysis. Besides, biologically, in no 2 patients can the evolution of atherosclerosis or its complications be strictly comparable. Statistics do permit such mathematical comparisons in randomized controlled trials (RCTs), but they can extract a hidden biological price (3).

First, contrary to the assertion that the "slower the heart rate, the greater the benefit" (1), heart rates below 50 beats/min cannot generally be claimed to promote overall cardiovascular integrity. Second, the negative inotropic action of beta-blockers has been ignored in this study (1) as well as in the CAFE (Conduit Artery Functional End Point) study (4). Any rise in central aortic pressure/pulse pressure by nonvasodilating beta-blockers would be intrinsically countered by their negative inotropic action. A pharmacologically reduced stroke volume would maximally affect central conduit vessels to reduce central vessel wall stress. Not surprisingly, atenolol reduces the elevated augmentation index in hypertensive patients compared with that in normotensive subjects (5). Third, the investigators (1) did not stratify their results according to age. An aging cohort is likely to have stiffer conduit arteries that, in turn, would exacerbate any differential drug effects on central aortic pressure (4). Fourth, the concept of dyssynchrony or uncoupling between outgoing and reflected aortic waves consequent to pharmacologically induced bradycardia (1) is purely speculative.

Cardiovascular morbidity and mortality are too complex to be resolved through multiple mathematics-based comparisons of diverse pharmacologic agents, particularly when polytherapy with several drugs might be involved. Moreover, all vasodilators usually worsen migraine headache; among antihypertensive agents, beta-blockers, however, do not generally aggravate headache. Regardless of age or race, hypertension is commonly associated with headache that has several features of migraine (6). Proscription of beta-blockers for initial or primary management of hypertension will increase the incidence of associated vascular headaches including migraine and make their management more complex. Next, beta-blockers hold center stage in management of predominantly systolic hypertension as well as the anxiety-related white coat hypertension/effect. Weight gain and precipitation of diabetes mellitus by beta-blockers is a relative risk unrelated to pancreatic islet cell damage.

In essence, this study (1) and the accompanying editorial (7) seek to convert a small-to-moderate statistical relative risk into an absolute biological risk with important practical implications. RCTs allow scientists to carry out credible research without having to discern crucial clinical phenomena or diminishing the need for the same (3). While using research tools such as RCTs or meta-analysis involving RCTs, we must remain cognizant of the intrinsic biological limitations of mathematical data mining. To seek or force a clinical/therapeutic consensus in the face of biological uncertainty cannot be commended as the best scientific/research practice.

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Beta-Blocker–Induced Heart Rate Reduction

Too Simplistic to Explain the Deleterious Effects of Beta-Blockers

In their recently published article, Bangalore et al. (1) concluded, from a meta-regression analysis of 9 studies including a total of 34,096 patients taking beta-blockers as first-line therapy and 30,139 patients taking other antihypertensive agents, that beta-blocker–associated reduction in heart rate increased the risk of myocardial infarction, cardiovascular events, and death for hypertensive patients. The authors suggested, as a mechanism, that "pharmacologically induced bradycardia leads to dyssynchrony or uncoupling between outgoing and reflected wave, thereby elevating central aortic pressure." They referred to the CAFE (Conduit Artery Functional End Point) study, which showed a higher central aortic systolic blood pressure after atenolol-based treatment than after amlodipine-based treatment, and to the main ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) study showing a better predictive value for cardiovascular events of amlodipine-based treatment than atenolol-based treatment. Although appealing, their conclusion that beta-blockers are deleterious through the reduction in heart rate, thus increasing central pulse pressure, may be too simplistic and not supported by data.

Indeed, although the authors pointed out that resting heart rate was an independent risk factor for cardiovascular morbidity and

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mortality for hypertensive patients, they did not analyze the influence of baseline heart rate in their meta-analysis, a major confounding factor. We performed a similar meta-regression analysis in the same set of studies. We first checked that we obtained similar results concerning the influence of heart rate, measured at the end of the trial in the beta-blocker group, on the relative risk of myocardial infarction (Fig. 3 of Bangalore et al. [1]): the equation derived from our analysis ($y = 2.593 - 0.0237x$; $p = 0.0072$) was very close to the equation ($y = 2.5794 - 0.0235x$; $p < 0.0001$) found by Bangalore et al. (1). We further analyzed the influence of heart rate, measured at baseline in the beta-blocker group, on the relative risk of myocardial infarction, and found a significant relationship ($y = 3.864 - 0.0380x$; $p < 0.0001$). The lower the heart rate at baseline, the higher the relative risk of myocardial infarction. Importantly, the slope of the later equation (baseline heart rate) was 1.6-fold higher ($p < 0.001$) than that of the former one (heart rate at the end of the trial). These results suggest that heart rate at baseline (i.e., before any administration of beta-blocker) is a better predictor of myocardial infarction than heart rate at the end of the trial. The relative risk for myocardial infarction was higher than unity when baseline heart rate was lower than 75.4 beats/min, and lower than unity when heart rate was higher than this value.

Thus, heart rate at baseline may have acted as a confounding factor in the analysis performed by Bangalore et al. (1). This suggests that reduction in heart rate may not be the main mechanism through which beta-blockers devoid of vasodilating properties, particularly atenolol, exert deleterious effects on the cardiovascular system, and demonstrate less effect than other antihypertensive agents for preventing cardiovascular events. Indeed, in contrast to vasodilating agents like calcium-channel blockers and renin-angiotensin system blockers, atenolol does not reduce total peripheral resistance and sympathetic drive, and fails to induce the long-term remodeling of large and small arteries that is required for structural improvement of arterial stiffness and resistance and the reduction in wave reflection and central aortic blood pressure.

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Beta-Blocker–Induced Heart Rate Lowering, Cardioprotection, and Hypertension

Bangalore et al. (1) have provided an intriguing observation that cardiovascular (CV) events, including CV death, myocardial infarction, heart failure, stroke, and all-cause death, may be increased in hypertensive patients placed on beta-blockers and that this may be related to the degree of heart rate reduction. They have done this by performing meta-regression analyses to demonstrate the relationship between heart rate and cardiovascular outcomes.

However, the data in their graphs show that the regression lines cross the line of unity. The 1 study that is consistently at or below unity in their graphs is the IPPSH (International Prospective Primary Prevention Study in Hypertension), which compared a beta-blocker with placebo. Similarly, the only other placebo-controlled trial analyzed, STOP (Swedish Trial in Old Patients with Hypertension) (2), shows a relative risk of about 0.9 in Figure 4 of Bangalore et al. (1). This suggests that beta-blockers are not increasing CV events because there is no increase in events in beta-blocker patients compared with placebo patients. The major differences in outcome rates are in the studies comparing beta-blockers with active controls.

These findings suggest that beta-blockers were less effective at preventing CV events than other antihypertensive agents. The mechanism for this may be evident in Table 2 of Bangalore et al. (1), which shows that beta-blockers resulted in less blood pressure reduction in 5 of 7 active control trials analyzed by the authors, with up to a 9.2-mm Hg difference in systolic blood pressure. This suggests that beta-blockers were simply less effective antihypertensive agents in general. Thus, an alternative interpretation of the authors' findings is not that beta-blockers increase mortality, as has been widely reported in the press, but that beta-blockers are simply less effective antihypertensive agents than diuretics or dihydropyridine calcium-channel blockers. As a result, they are also less effective at preventing hypertension-related cardiovascular events than other medications. The clinical message I would take from this study is that we must remember that the primary goal of antihypertensive treatment is to lower blood pressure and not to lower heart rate.

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